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Enantioselective Synthesis of SSR 241586 by Using an Organo-Catalyzed Henry Reaction

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ABSTRACT

An organo-catalyzed Henry reaction, applied to an α-keto ester, has allowed the enantioselective synthesis of SSR 241586, a 2,2-disubstituted morpholine active in the treatment of schizophrenia and irritable bowel syndrome (IBS).

Substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) are the best known members of the tachykinin neuropeptide family which activity is mediated by at least three distinct receptors: NK1 (SP-prefering), NK2 (NKA-prefering), and NK3 (NKB-prefering). Due to their pharmacological effects on pain, on the central and peripheric system, as well as on the gastrointestinal and urogenital tracts, antagonists of NK receptors have attracted considerable attention as potentially powerful therapeutic agents. Among them, the optically active 2,2-disubstituted morpholines SSR 241586 and SSR 240600, developed by Sanofi-Aventis, were shown to be active in the treatment of depression, schizophrenia, urinary trouble, emesis, and irritable bowel syndrome (IBS) (Figure 1).

So far, the methods reported to isolate the appropriate isomer of the 2,2-disubstituted morpholine include crystal-

lization with d-tartaric acid, Sharpless dihydroxylation (AD-mix β), asymmetric epoxidation of a homoallylic alcohol catalyzed by Zr(O-t-Bu)₄ and diisopropyl d-tartrate, as well as asymmetric cyanosilylation of a ketone using a Lewis acid/Lewis base bifunctional catalyst.

Here, we disclose an enantioselective synthesis of SSR 241586 using an organo-catalyzed Henry reaction to control the quaternary stereogenic center of (R)-configuration present at C2 in the
The synthesis of SSR 241586 started with the transformation of commercially available ethyl chlorooxoacetate (1) to ethyl α-oxo-1H-imidazole-1-acetate (2). When 2 was treated with 3,4-dichlorophenylmagnesium bromide, the desired α-keto ester 3 was isolated in 74% yield. An organocatalyzed Henry reaction was subsequently applied to α-keto ester 3. Quinine-derived compound A was chosen as the appropriate catalyst due to its ability to furnish Henry adducts with high enantiomeric excess on a broad range of substrates. Thus, treatment of 3 with nitromethane (10 equiv) in the presence of catalyst A (5 mol %) in CH₂Cl₂ at −20 °C produced β-nitro alcohol 4 in 76% yield and with an enantiomeric excess of 96% (Scheme 2).

The synthesis of the morpholine ring was achieved in four steps from nitro alcohol 4. At first, this latter was selectively reduced to the corresponding amino alcohol 5. Under hydrogenation conditions, using Raney nickel (H₂, Raney Ni/EtOH), a retro-Henry reaction was observed. On the contrary, when the reduction of the nitro group was performed using zinc dust in acetic acid, the amino alcohol 5 was isolated without any racemization. N-Acetylation of the resulting primary amine (CICH₂COCl, Et₃N, CH₂Cl₂, rt, 4 h) produced amide 6 (99%) which, after treatment with NaH, afforded the cyclic amide 7 in 75% yield and with an enantiomeric excess of 96%. The amide and ester groups were reduced by BH₃·THF (6 equiv, THF, reflux, 3 h) to produce the 2,2-disubstituted morpholine 8 in 88% yield (Scheme 3).

In order to synthesize SSR 241586, compound 8 has to be transformed to its homologue 11. Thus, 8 was treated with di-tert-butyl dicarbonate (Boc₂O, Et₃N, MeOH, rt, 16 h) to produce the N-protected morpholine 9 (93% yield). An oxidation step [Dess–Martin periodinane (DMP), CH₂Cl₂, rt, 1 h] followed by a Wittig reaction (KHMDS, BrPPh₃CH₃, THF) provided olefin 10 (82% for the two steps), and after an oxidative hydroboration (BH₃·Me₂S, then H₂O₂, NaOH), alcohol 11 was isolated in 64% yield. In order to introduce the N-benzoyl group present in the final product, a deprotection/protection step was achieved. Thus, N-tert-butyli carbamate 11 was treated with TFA (CH₂Cl₂, rt, 1 h), and the resulting morpholine was then transformed into the N-benzoylmorpholine 13 (PhCOCl, Et₃N, CH₂Cl₂, rt, 1.25 h) in 45% yield (for the two steps) (Scheme 4).

We have to point out that the straightforward access to SSR 241586 from 8, by transforming the latter in N-benzoylmorpholine, was not possible. Indeed, after transformation of 8 to N-benzoylmorpholine 9, this compound was converted to olefin 10' in two steps (DMP, CH₂Cl₂; BrPPh₃CH₃, t-ButOK, THF), but unfortunately, the oxidative hydroboration of 10' was not successful as 13 was not formed (Scheme 5).

The formation of SSR 241586 was completed from 13 in two steps. After mesylation (MsCl, Et₃N, CH₂Cl₂, rt, 1 h) and treatment of the resulting mesylate with piperidine SSR

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**Scheme 1. Retrosynthesis of SSR 241586**

![Scheme 1](image)

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**Scheme 2. Synthesis of the Optically Active Intermediate (R)-4**

![Scheme 2](image)
By using an organo-catalyzed Henry reaction, SSR 241586 was synthesized in 15 steps with an excellent enantiomeric excess. As this method is versatile, a number of optically active 2,2-disubstituted morpholine analogues of SSR 241586 could be obtained.

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**Supporting Information Available:** Experimental procedure and characterization data of compounds 2–13 and SSR 241586. This material is available free of charge via the Internet at http://pubs.acs.org.

241579 [N,N-dimethyl-4-(piperidin-1-yl)piperidine-4-carboxamide][11] under basic conditions (K₂CO₃, DMF/CH₃CN 1:1, 100 °C, 3 h), the desired SSR 241586 was isolated in 48% yield (two steps) with an enantiomeric excess of 93% (Scheme 6).[12]